Poster 15: BMI1 Mediation of Chemoresistance through DNA Damage Repair Mechanisms in a Patient-Derived Ovarian Cancer Cell Line

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Topic
Ovarian

Objectives
To characterize the effects of BMI1 expression and platinum chemoresistance in a patient-derived ovarian cancer cell line and to investigate the potential mechanisms by which BMI1 may contribute to chemoresistance.

Methods
A patient-derived high grade serous ovarian cancer (HGSOC) cell line was treated with serial cisplatin exposure to generate cisplatin-resistant (CR) and sensitive (SE) sublines. RNA-seq, qPCR and western blotting were used to measure the levels of BMI1 expression in these cells. BMI1 overexpression and knockdown were achieved using lentiviral delivery of a GFP-tagged BMI1 vector and shRNA targeting BMI1, respectively. Cell viability and IC50 levels, the concentration at which 50% cell death occurred, were determined by MTT assays. Cells were exposed to ionizing proton radiation at 4 Gy and immunofluorescence (IF) was performed to visualize the location of BMI1 and Rad51.

Results
RNA-seq revealed significant upregulation of BMI1, along with other stemness factors, in the CR compared to SE subline and the IC50 of CR was 10x that of the SE. BMI1 overexpression and knockdown did not reliably change BMI1 expression on the mRNA or protein level. No difference in IC50 was therefore detected for these virally transduced cells. On IF, BMI1 is predominantly located in the cytoplasm. After exposure to ionizing radiation, BMI1 migrates intranuclearly and co-localizes with Rad51, an essential protein involved with repairing DNA double-strand breaks.

Conclusions
BMI1 is a stem cell factor implicated in regulating chemoresistance. In our model, we found that a chemoresistant subline of a patient-derived HGSOC cell line had elevated levels of BMI1 compared to the sensitive subline. On immunofluorescence, BMI1 translocates intranuclearly and co-localizes with Rad51, suggesting a functional role of BMI1 in homologous recombination and thereby providing a framework in explaining how BMI1 may contribute to cisplatin chemoresistance in ovarian cancer.

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